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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/432,906	11/02/1999	ALEXANDER BAGUISI	1322.1032-001	1763

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 11/30/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/432,906	BAGUISI ET AL.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-9,11-17,19-26 and 28-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-9,11-17,19-26 and 28-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *15* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The office action mailed November 28, 2001 in paper no. 16 is vacated. A new office action on the merits appears below.

Applicant's arguments filed August 15, 2001 in paper no. 14 have been fully considered but they are not persuasive. The amendment has been entered. The pending claims are 1,2,4,5,7-9,11-17,19-26 and 28-59.

Applicant's statements regarding priority are noted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2,4,5,7-9,11-17,19,20, and 39-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the methods of cloning a mammal, methods of cloning a transgenic mammal, comprising introducing a G1 nucleus from an activated donor cell into an activated oocyte of the same species in telophase II of meiosis or an enucleated oocyte of telophaseII meiotic structure to form a mammalian reconstructed embryo, fusing the reconstructed embryo and transferring the embryo to a recipient mammal of the same species to produce a mammal as claimed and a method of producing a mammalian nuclear transfer embryo, comprising combining a G1 nucleus from a somatic activated donor cell with an activated, enucleated oocyte in telophase II and of the same species as the donor cell, and fusing the nucleus and oocyte, to thereby for a nuclear transfer embryo, does not reasonably provide enablement for the methods as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Fusion is required for the integration of the oocyte and donor nucleus or donor cell membranes. Without fusion the membranes of the donor nucleus or donor cell would remain intact and the donor nucleus would not be available for reprogramming by the cytoplasm of the enucleated oocyte recipient.

Should this be the case, then embryo development would fail. As fusion is disclosed as a distinct step in the specification, it is appears to be critical to the invention and must be included. See specification pages 11,12 and 31-33. Further, successful nuclear transfer requires that the donor nucleus be diploid. The at taught at the time of filing, the only nuclei that are diploid are those in G0 or G1 phases of the cell cycle. S/M and G2 are not so recognized by the art. See WO 97/07668 (Campbell) page 7, line 16 to page 8, line 11. Further at the time of filing, the art taught that nuclear transfer technology was unpredictable. Westhusin teaches that "the methods utilized for cloning one species of animal do not automatically apply across different species" (page 36, parag. 4, lines 2-4). Westhusin further states that it is the efficiency of the six steps listed, all of which vary between species, that ultimately affects the ease at which any particular animal can be cloned (pages 36-37, bridg. Sent.). Thus, for these reasons, the invention as claimed would require an undue amount of experimentation on the part of the skilled artisan without a predictable degree of success.

Claims 21-26 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a heterologous protein in the milk of a cloned transgenic mammal comprising transferring into an enucleated telophase II oocyte or an enucleated oocyte of telophase II meiotic structure a G1 nucleus of the same species as the donor, an activated somatic cell from a transgenic mammal comprising a milk protein promoter operatively linked to a DNA sequence encoding a protein of interest, fusing the oocyte and donor nucleus, as claimed, does not reasonably provide enablement for the methods where the donor cells are transformed in vitro prior to the nuclear transfer procedure into an enucleated oocyte in telophase II. The discussion of mammals, G1 and fusing as limitations are discussed above and transferred to this rejection. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, the art was replete with discussion and dialog concerning the production of transgenic non-human animals. Transgenic animals were regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the

genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Additionally, □the position effect□ and unidentified control elements also were recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). The elements of the particular construct used to make transgenic animals were held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) Journal of Biotechnology, constructs, page 275, col. 1, parag. 1). The specification does not provide any guidance on any promoters or other expression regulatory sequences that when placed in operative association with a DNA sequence encoding a heterologous protein, that the cloned ungulate will produce a protein of interest in its milk, blood, urine, hair, mammary gland, muscle or viscera for the breadth of the claims. The art at the time of filing had significant teachings concerning the mammary gland as a bio-reactor, but not any other body fluid. There were no correlative teachings in the art concerning other body fluid promoters that would overcome any unpredictability associated with □biofarming□. Further, at the time of filing, Fulka et al, or record, stated that the cloning of adult mammals is very inefficient and highly unpredictable (page 849, col. 1, lines 9-10 and page 850-851, bridg. sent.). Thus for these reasons the claims are not seen as enabled by the specification. The skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31,32 and 34 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The media surrounding was altered as evidenced by the inclusion of Hoechst 33342 (page 31, col. 1, parag. 2, lines 8-11). Thus, Bordignon clearly anticipates the claimed invention.

Claims 35,36 and 38 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The oocytes were activated by exposure to ethanol (page 30, col. 2, parag. 1, lines 1-11). Thus Bordignon clear anticipates the claimed invention.

Applicant argues that cytochalasin B is used to soften the cell membrane of oocytes. Applicant argues that there is no disclosure that cytochalasin B had any effect on the meiotic spindle apparatus. These arguments are not persuasive.

As evidence for the examiner's rejection, Kono teaches that cytochalasin B inhibits microtubule polymerization. As the meiotic spindle is composed of microtubules, incubation with cytochalasin B would destabilize the meiotic spindle apparatus. Thus, despite the teachings of the reference and applicant's arguments regarding cytochalasin B's role in softening the cell membrane, the art at the time of filing clearly taught that cytochalasin B inhibits microtubule formation and thus would inhibit or destabilize the meiotic spindle.

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31,33,35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bordignon et al (1998) Molec. Reprod. Devel. 49, 29-36 in view of Kono (1997) Rev.of Reproduction 2, 74-80 and Molecular Biology of the Cell, 2nd ed., Alberts et al, Garland Publishing, Inc., pages 652-653.

Bordignon et al teach the enucleation of telophase nuclei, which have a mitotic spindle apparatus, by incubating the nuclei in cytochalasin B (page 31, col. 1, parag. 1, line 3-6; parag. 2, lines 1-15; and col. 3, parag. 1, line 1 to page 32, line 5). Both the meiotic spindle apparatus and chromosomes were destabilized as evidenced by fragmented chromatin in the first polar body (page 31, fig.1, legend). The oocytes were activated by exposure to ethanol (page 30, col. 2, parag. 1, lines 1-11). However, Bordignon does not teach destabilization of the meiotic spindle apparatus using demecolcine, nocodazole, colchicine or paclitaxel. Kono teaches that nocodazole inhibits tubulin polymerization and thus this compound would destabilized the meiotic spindle apparatus (page 74, col. 2, parag. 1, lines 3, and 8-11). Also, Molecular Biology of the cell teaches that colchicine and paclitaxel, also known as tactual, are destabilizes of tubulin and thus the meiotic spindle apparatus (page 652, parag. 4 to page 653, parag. 3 and Table 11-3). Demecolchicine is a colchicine is a derivative of colchicine having the same destabilizing property on tubulin as colchicine and would obvious perform the same function as colchicine. Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to substitute any tubulin destabilizing agent for cytochalasin B which functions to destabilize chromosomes and controls by destabilizing actin of microfilaments. Motivation is provided by Bordignon stating that their method provides for enucleation without the use of DNA strains or UV irradiation with a result of great blastocyst achievement (page 34, col. 1, parag. 1). There is sufficient motivation and teachings in the prior art to provide a reasonable expectation of success.

Applicant argues that cytochalasin B is used to soften the cell membrane of oocytes. Applicant argues that there is no disclosure that cytochalasin B had any effect on the meiotic spindle apparatus. These arguments are not persuasive.

As evidence for the examiner's rejection, Kono teaches that cytochalasin B inhibits microtubule polymerization. As the meiotic spindle is composed of microtubules, incubation with cytochalasin B would destabilize the meiotic spindle apparatus. Thus, despite the teachings of the reference and applicant's arguments regarding cytochalasin B's role in softening the cell membrane, the art at the time of filing clearly taught that cytochalasin B inhibits microtubule formation and thus would inhibit or destabilize the meiotic spindle.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th and Tu-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda can be reached on 703-305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
November 28, 2001